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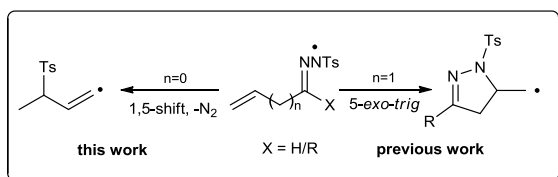
Visible Light Photocatalytic Transformation of α,β -Unsaturated-N-Tosylhydrazones: a Novel Route to Allylic Sulfones

Stefano Parisotto, Gabriele Garreffa, Carlo Canepa, Eliano Diana, Francesco Pellegrino, Emanuele Priola, Cristina Prandi, Valter Maurino* and Annamaria Deagostino*.

In this paper, the first example of a visible light driven transformation of α,β -unsaturated sulfonylhydrazones to allylic sulfones is described. The reaction is carried out in very mild conditions affording allylic sulfones by generation of highly delocalized radicals, crucial in promoting nitrogen loss instead of the commonly observed intramolecular hydroamination. Moreover, the mechanism has been investigated demonstrating the generation of a vinyl radical intermediate.

Tosylhydrazones are useful synthetic intermediates that have been used in organic chemistry for many years for the production of transient diazo compounds by base promoted elimination of toluenesulfinate. The diazo compound can be further decomposed to carbene on heating,^[1] or afford a vinyl lithium derivative in the presence of alkyl lithium bases (Shapiro reaction).^[2] In alternative, the *in situ* generation of diazo compounds can be achieved from isolating tosylhydrazone salts.^[3] More recently their ability to generate reactive metal carbenes has triggered renewed interest in these reagents. In 2007 Barluenga and co-workers reported the first example of tosylhydrazones used as nucleophilic partners in Pd-catalyzed cross-couplings^[4] which are complementary to the Shapiro reaction and carbonyl compound cross-coupling, normally achieved *via* triflates, to afford olefins.^[5] Many examples of the above cited reactivity have been reported,^[6] also using Cu,^[7] Rh^[8] or Ni.^[9] Moreover some attention was given to the photolytic decomposition of tosylhydrazone alkali metal salts.^[10] Several patterns were observed depending on the reagent structure. For example, the irradiation of cyclopentylideneacetaldehyde tosylhydrazone afforded spiro[2.4]hept-1-ene, vinylidenecyclopentane and 1-vinylcyclopentene by direct intramolecular rearrangements from the diazoalkene excited state,^[11] whereas dihydropyrazoles were obtained from β,γ -unsaturated hydrazones, probably *via* an intramolecular single electron-transfer (SET).^[12] Very recently, a visible-light induced version of this process on tosylhydrazones provided hydroamination products in good yields *via* the deprotonation of sulfamido group and photocatalytic oxidation to a neutral N-centered which also exploited a TEMPO promoted cascade reaction.^[13] In this context, visible-light photocatalysis has recently emerged as powerful reaction manifold for chemical synthesis^[14]. This activation mode enables the transformation of visible light energy into chemical potential. Thereby, it represents a greener and more sustainable route toward solar energy driven synthetic processes.^[15] Moreover, light activation represents a convenient and selective switch for controlling chemical processes. Indeed, it has the ability to easily generate reactive radical or ionic species, giving access to reaction pathways complementary to those promoted *via* thermal conditions.^[14, 16] This approach is possible thanks to the presence of metal polypyridyl photocatalysts, such as the complex tris(2,2'-bipyridine) ruthenium(II), which absorb visible light to give relatively long-lived photoexcited triplet states, or organic photosensitizers such as Eosin Y.^[17] As valuable examples, the work of MacMillan,^[18] Yoon,^[19] Stephenson^[20] research groups must be cited.

Recently, we were interested in studying the photoinduced reactivity of α,β -unsaturated tosylhydrazones, and comparing it with that of non-conjugated alkenyltosylhydrazones. Surprisingly we observed the formation of allylic sulfones (Scheme 1), by loss of a nitrogen molecule together with an apparent sulfonyl group 1,5-shift, under mild conditions.



Scheme 1 Visible light photoinduced reactivity of α,β - and β,γ -unsaturated tosylhydrazones

Sulfones have emerged as important synthetic targets in recent years, they exhibit interesting chemical properties^[21] and are useful intermediates in organic synthesis. Moreover the sulfonyl motif is present in many natural products and pharmaceutical compounds,^[22] for this reasons it has drawn much attention over the years.^[23] Their preparation is classically based on the oxidation of corresponding sulfides or by displacement reactions using sulfinates as nucleophiles.^[24] However, these methods generally involve drawbacks such as limited substrate sources, including tosylhydrazones, which require harsh reaction conditions.^[25]

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by Hu et al.^[13a], where 1.5 eq. of NaOH and 2% mol of [Ru(bpy)₃]Cl₂·6H₂O were used with respect to (*E*)-but-2-enal-*N*-tosylhydrazone (**1a**) that was chosen as a model. The reaction was carried out in 5 mL of CHCl₃ and a Philips PL-S 9W 52 2p fluorescent blue lamp was used as a light source (entry 1). Surprisingly after 16 h, a very clean crude product was recovered, corresponding to 4-(1-methylallylsulfonyl)-toluene (**2a**, 35% yield). Encouraged by this unexpected result, we investigated the role of the base, solvent and photosensitizer on the reaction, the results are described in Table 1.

Table 1: Photocatalytic conversion of (*E*)-but-2-enal-*N*-tosylhydrazone (**1a**)^a

Entry	Base	Catalyst	Solvent	Time (h)	Conv., Yield (%) ^b
1	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	100, 35
2	NaOH	-	CHCl ₃	16	0, 0
3	-	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	0, 0
4 ^c	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	0, 0
5	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CH ₂ Cl ₂	16	0, traces
6	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	MeCN	16	50, 20
7	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	MeOH	16	60, 25
8	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	DMSO	16	100, decomp.
9	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	DMF	16	0, 0
10	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	THF	16	30, 10
11	NaOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃ ^d	16	100, 28
12	KOH	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	100, 38
13	an. K ₂ CO ₃	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	100, 41
14	Cs ₂ CO ₃	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	100, 37
15	NaHCO ₃	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃	16	0, 0
16	an. K ₂ CO ₃	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O	CHCl ₃ /DMF	4	100, 41
17 ^e	an. K ₂ CO ₃	EOSIN Y	CHCl ₃ /DMF	16	100, 18
18	an. K ₂ CO ₃	[Ru(bpz) ₃]PF ₆	CHCl ₃ /DMF	16	100, 0
19 ^f	an. K ₂ CO ₃	[Ir(ppy) ₂ (dtbbpy)]PF ₆	CHCl ₃ /DMF	16	100, 15

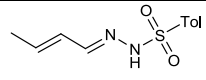
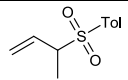
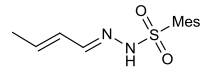
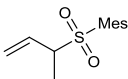
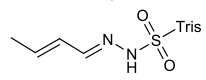
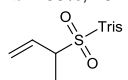
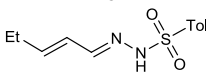
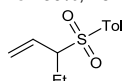
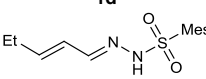
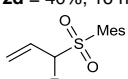
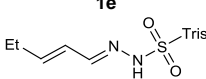
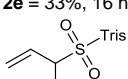
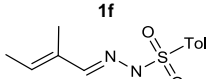
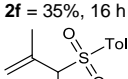
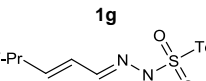
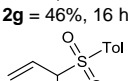
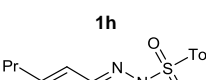
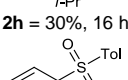
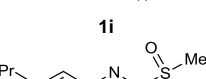
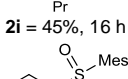
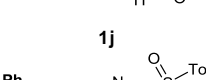
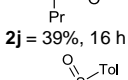
^a Reactions conditions: tosylhydrazone 0.3 mmol, base 0.45 mmol, anhydrous solvent 5 mL, catalyst 0.06 mmol (2%) ^b Determined by NMR using nitromethane as internal standard. ^c Reaction performed in the dark. ^d CHCl₃ with the addition of 50 μ L of water. ^e 550 nm light source. ^f 405 nm light source

basic NaHCO₃ was completely inefficient (entry 15), for its inability to deprotonate the tosylhydrazone. At last, other photosensitizers were tested: EOSIN Y was firstly used and **2a** was obtained in 18% yield (entry 17), whereas [Ru(bpz)₃]²⁺ caused the consumption of (**1a**) but a mixture of by-products was recovered (entry 18).^[14] No improvement was registered when [Ir(ppy)₂(dtbbpy)]PF₆ was used (entry 19). The conditions described in entry 16 of **Table 1** were chosen for studying the scope of the reaction. It must be underlined that in this process a total conversion of the reactant, that affords the corresponding 4-(1-methylallylsulfonyl)-toluene (**2a**) in moderate yields, was obtained. Nevertheless, a LC-MS analysis of the crude prior to work up revealed para-tolylsulfonate in ratio of 1.5 to 1 respect to **2a**, suggesting a side reaction, which gives a sulfinic derivative, further oxidized to the corresponding sulfonic acid.^[26]

The photocatalytic nature of the process was confirmed by the recovery of **1a** when reacted both in the absence of the Ru complex (entry 2) or in the dark (entry 4), the same result was obtained with no base introduced in the reaction milieu (entry 3), suggesting the tosylhydrazone anion as actual reactant. Then the solvent influence was studied. Only traces of product **2a** were recovered with the unreacted tosylhydrazone **1a** when aprotic CH₂Cl₂ was used (entry 5), a similar result was obtained in DMF (entry 9), whereas a total decomposition of the starting material was observed in DMSO (entry 8). THF afforded a little amount of **2a** (10%) but, again, most of **1a** was recovered (entry 10), similarly to the weakly protic MeCN (entry 6). These findings suggest that both the polarity and ability of donating H atom strongly influence the reaction outcome. Indeed, the use of MeOH afforded the product **2a** in lower yield (25%) and a 60% conversion (entry 7) with respect to CHCl₃, maybe due to MeOH higher acidity. CHCl₃ demonstrated itself to be an optimal solvent, moreover the reaction rate increased when a mixture of CHCl₃/DMF (50/50) was used, affording the product in comparable yield respect to CHCl₃ alone (41%). DMF was chosen because it allowed a clear and homogeneous solution to be obtained and seemed to be inert in the reaction conditions, as shown in entry 9. The reaction was carried out also adding 50 μ L of water to CHCl₃ (entry 11), affording **2a** in lower yield, thus demonstrating water tolerance but the need for anhydrous medium. The base effect was elucidated, KOH efficiency was comparable to NaOH, (entry 12), afterwards we turned to anhydrous K₂CO₃, and a total conversion of the reactant was observed (41% yield), despite the weaker basicity with respect to NaOH (entry 13), whereas Cs₂CO₃ was not efficient (37% yield, entry 14). Finally the less

The reaction was then extended to several enal-arylsulfonylhydrazones, the results are reported in Table 2.^[27] The migrating moiety and substitution of the alkyl chain influence were investigated. The chain length and branching or a α -methyl group did not influence the reaction outcome, as demonstrated by **2a**, **2d**, **2i** and **2g** respective yields. A phenyl group in the β position decreased the reaction rate, maybe for the higher stability of the corresponding anion. As migrating group the tosyl moiety was compared to mesityl- and trisylsulfonyl groups pointing out the role of the steric hindrance (**2b**, **2c** respect to **2a**, **2e**, **2f** respect to **2d**).

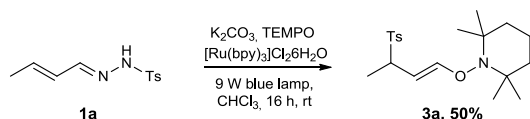
Table 2: scope of photocatalytic transformation of α,β -unsaturated hydrazones.^{a,b}

$\text{R}^1\text{---CH=CH(R}^2\text{)---N=N---SO}_2\text{Ar} \xrightarrow[\text{9 W blue lamp, CHCl}_3/\text{DMF, rt}]{[\text{Ru}(\text{bpy})_3]\text{Cl}_2\cdot 6\text{H}_2\text{O, K}_2\text{CO}_3} \text{R}^1\text{---CH(SO}_2\text{Ar)---CH(R}^2\text{)=CH}_2$	
1a - 1k	2a - 2k
Reagent	Product (yield, time)
 1a	 2a = 41%, 16 h
 1b	 2b = 35%, 16 h
 1c	 2c = 39%, 16 h
 1d	 2d = 40%, 16 h
 1e	 2e = 33%, 16 h
 1f	 2f = 35%, 16 h
 1g	 2g = 46%, 16 h
 1h	 2h = 30%, 16 h
 1i	 2i = 45%, 16 h
 1j	 2j = 39%, 16 h
 1k	 2k = 39%, 16 h
Tol (tosyl) Mes (mesityl) = 2,4,6-trimethylphenyl Tris (trisyl) = 2,4,6-triisopropylphenyl	

^aReaction conditions: tosylhydrazone 0.3 mmol, K₂CO₃ 0.45 mmol, anhydrous CHCl₃/DMF 5 mL, [Ru(bpy)₃]Cl₂·6H₂O 0.06 mmol (2%)

^bDetermined on isolated product

To verify if a C-centered radical is involved as a key intermediate during the process and might be trapped by radical quenchers, the model reaction was carried out in the presence of TEMPO (2.0 equiv) affording (*E*)-2,2,6,6-tetramethyl-*N*-(3-tosylbut-1-enyloxy)-piperidine **3a** in 50% yield (Scheme 2, for X ray structure see SI). This finding suggests that the process involves a vinyl radical intermediate, which finally gives the allylic sulfone *via* H abstraction presumably coming from the solvent.



Scheme 2 Addition of TEMPO to the model reaction

To explore the solvent's active role, (*E*)-but-2-enal-*N*-tosylhydrazone **1a** was reacted in CDCl₃. A mixture of two deuterated isomers (**4a** and **4b**, Scheme 3) was obtained, thus suggesting CHCl₃ as the only H source. Surprisingly, derivative **2a** was not generated, as demonstrated by the lack of methylenic signals in DEPT spectrum and by LC-MS. The NMR analysis of signals related to the CHD group allowed the isomer ratio determination, moreover the increased multiplicity of vinyl protons in **4a** and **4b** respect to **2a**, confirmed the deuterium incorporation.

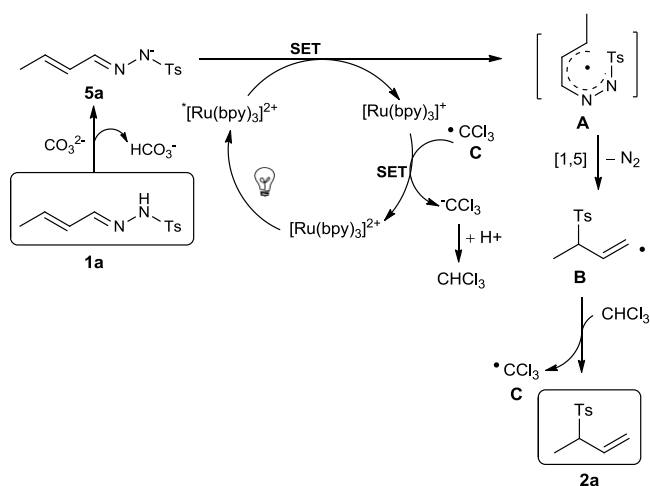


Scheme 3 Deuterium labeling

To exclude the possibility of a chain radical mechanism, experiments were carried out in the presence of radical initiators: no reaction was induced when AIBN was used both at rt and 80°C, whereas the more reactive benzoyl peroxide produced a mixture of degradation by-products (see SI).

As already reported in literature and described above, the tosylhydrazone anion is the actual quencher (see entry 3, table 1). As a matter of fact the quenching is clearly detectable by eyes in the reaction medium. Just after the dissolution of tosylhydrazone and [Ru(bpy)₃]²⁺ a red luminescent glow, which vanishes after 5-10 minutes of base addition, is clearly visible. A series of luminescence-quenching experiments were accomplished to support the hypothesis that the anion **5a** might be initially oxidized by the excited state of the photocatalyst. Indeed, no luminescence quenching was observed when solutions at increasing concentrations of **1a** were analyzed. On the contrary a significant decrease of [Ru(bpy)₃]²⁺ luminescence was observed when the potassium salt **5a** was utilized (see SI, Figure 7). Likely, an ion pair of **5a** with the photosensitizer forms, inducing a luminescence static (in addition to the dynamic) quenching. Their coexistence is confirmed by the non linear trend of the Stern-Volmer plot (see SI, Figure 8).

A plausible mechanism is finally described in Scheme 4. Deprotonation of tosylhydrazone **1a** occurs under basic conditions to afford the anion **5a**. Its single-electron oxidation by the excited state of the photocatalyst (^{*}[Ru(bpy)₃]²⁺) gives the *N*-centered radical **A**, where the spin density is delocalized over the conjugated system. Nitrogen loss affords the vinyl radical **B** *via* a formal sulfonyl group 1,5-shift, possibly through a six membered cyclic intermediate. **B** readily abstracts an H atom from the solvent giving the product **2a** together with CCl₃ radical **C**, which regenerates the photocatalyst [Ru(bpy)₃]²⁺ through a SET process. Alternatively, [Ru(bpy)₃]⁺ can start a reductive dehalogenation of CHCl₃.^[14, 28]



Scheme 4 Mechanism hypothesis

In conclusion, we studied the behavior of α,β -unsaturated tosylhydrazones in visible light photocatalyzed reactions. This strategy provides a novel route to access allylic sulfones in very mild conditions. Preliminary studies on the reaction mechanism are presented, investigations to extend the reaction and get more insights into the mechanism are underway.

Keywords: visible light, photocatalysis, α,β -unsaturated tosylhydrazones, allyl sulfones, hydrazonyl radicals.

□

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